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Risk of subarachnoid haemorrhage according to number of affected relatives: a population based case–control study

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Relatives of patients with aneurysmal subarachnoid haemorrhage (SAH) have an increased risk of this type of stroke. In a population-based study, we analysed individualized risks of SAH according to the number of affected first-degree relatives. We retrieved all patients diagnosed with SAH in 2001–05 from the Swedish Inpatient Register. For each of the 5282 patients, we identified five controls ($n = 26\,402$) through the nationwide Register of Total Population. Through the Multi-generation Register, we retrieved all first-degree relatives for patients and controls and checked whether these 130\,373 relatives had been diagnosed with SAH. By means of conditional logistic regression, we calculated odds ratios with corresponding 95% confidence intervals (95% CI) for the risk of SAH according to the number of affected relatives, and to the gender, age and type of kinship of the patient and affected relative. The odds ratio of SAH for individuals with one affected first-degree relative was 2.15 (95% CI 1.77–2.59). For individuals with two affected first-degree relatives, the odds ratio was 51.0 (95% CI 8.56–1117). Gender, age and type of kinship did not influence the risk for individuals with one or more affected relatives. The risk of SAH is slightly increased in the cases with one, but strongly increased in cases with two or more affected first-degree relatives. The latter strongly increased risk corresponds to a considerable absolute life-time risk of SAH and underscores the need to consider screening for aneurysms in these individuals.

Keywords: subarachnoid haemorrhage; aneurysms; population based; epidemiology; family study

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Introduction

Subarachnoid haemorrhage (SAH) from a ruptured aneurysm is a rare but devastating subset of stroke (Hop *et al.*, 1997; Hackett *et al.*, 2000; Inagawa, 2001; Stegmayr *et al.*, 2004; Koffijberg *et al.*, 2008) that occurs at a relatively young age. Individuals have an increased risk of SAH if a first-degree relative has had one (Ronkainen *et al.*, 1993; Bromberg *et al.*, 1995; Schievink *et al.*, 1995; Gaist *et al.*, 2000; Teasdale *et al.*, 2005; Sundquist *et al.*, 2007). The prevalence of unruptured aneurysms in individuals with one first-degree relative with SAH is slightly increased compared with those without first-degree relatives with SAH (Raaymakers and MARS study group, 1999). The prevalence

of unruptured aneurysms is even higher in individuals with two or more affected relatives (Ronkainen *et al.*, 1997; Wermer *et al.*, 2003). However, the actual risk of SAH in individuals with two or more relatives with SAH is unknown since families with two or more affected first-degree relatives are very rare. Moreover, individuals from these families may nowadays ask for screening and preventive treatment of asymptomatic aneurysms, which may affect the natural history. A study on the familial risk of SAH in Scotland found a trend towards an increasing risk of SAH as more and more closely related relatives experienced an SAH (Teasdale *et al.*, 2005). However, the increased risk was not statistically significant, probably because of the small

number of patients with two or more affected first-degree relatives with SAH. Recently, the risk of SAH in siblings was studied in the Swedish population (Sundquist *et al.*, 2007). A risk ratio of 2.75 was found for siblings of SAH patients. However, this study was too small to assess the risk of multiple affected relatives. We performed a population based case-control study in the Swedish population to assess the risk of SAH according to the number of affected relatives and type of kinship.

Material and Methods

Cases and controls

The patients in this patient-control study were identified from the Swedish Inpatient Register 1964–2006 (Anonymous, 1998) that contains individual-based information on discharges from inpatient care coded according to International Classification of Diseases (ICD) [versions 7–10], with a population-based (county-wise) coverage that encompassed 80% of Sweden in the mid-1970s and 100% since 1987. We included patients admitted to a hospital between 2001 and 2005 with SAH as the primary diagnosis, who were 15 years or older and who had no prior admission with SAH as either primary or secondary diagnosis in the Inpatient Register. Through the nationwide Register of Total Population, which since 1969 comprises the Swedish Census Register, we matched five controls to each case based on sex, year of birth, marital status and county of residence in the year of the index patient's admission with SAH. This selection yielded 5282 cases and 26 402 controls. For eight cases we were not able to provide all five controls.

Family members

The Swedish Multi-generation Register (Anonymous, 2006) includes information on parent-offspring relations for Swedish citizens born in 1932 or later. For both cases and controls, we retrieved all first-degree relatives (parents, children and siblings). For patients and controls born before 1932, the family history could only be provided by children and siblings. This selection yielded 21 724 relatives for cases and 108 649 relatives for controls, in total 130 373 first-degree relatives.

Assessing family history

For all the 130 373 identified relatives, all records were retrieved from both the Swedish Inpatient Register and the Cause of Death Register. The latter register includes details on causes of death

in patients who died without being admitted to the hospital. A relative was defined as being affected by SAH when either an admission to a hospital with a primary or secondary diagnosis of SAH was recorded or when the underlying or contributing cause of death of the relative was SAH. We only considered events that occurred before the date of the SAH of a case or the corresponding time for the controls.

Data analysis

Using conditional logistic regression, we calculated odds ratios with corresponding 95% confidence intervals (CIs) for the risk of SAH according to the family history. Due to small observed numbers, exact mid-*P* corrected 95% CIs were calculated when assessing the risk associated with having more than one affected relative. We aggregated counties into three regions for analysis: northern, central and southern Sweden. The risk associated with family history in relation to the individuals' sex, age at diagnosis and region was assessed by means of stratification.

Results

Tables 1 and 2 show the baseline characteristics of the 5282 patients and the 26 402 controls. The odds ratios of SAH for individuals with one or more affected first-degree relatives was 2.28 (95% CI 1.89–2.74). Compared with

Table 2 The odds ratio for having family history, defined as one or more affected first degree relatives, compared to no family history in relation to characteristics of the person at risk

	SAH patients <i>n</i> = 5282	Controls <i>n</i> = 26 402	Odds ratio	95% CI
Gender				
Male	2169 (41%)	10 834 (41%)	1.84	1.33–2.53
Female	3113 (59%)	15 568 (59%)	2.56	2.04–3.22
Age (years)				
15–49	1251 (24%)	6250 (24%)	1.92	1.33–2.76
50–59	1318 (25%)	6592 (25%)	2.27	1.64–3.15
60–69	1131 (21%)	5654 (21%)	2.64	1.86–3.74
≥ 70	1582 (30%)	7906 (30%)	2.40	1.44–3.99
Geographical region				
Northern	603 (11%)	3013 (11%)	2.64	1.55–4.49
Central	2132 (40%)	10 659 (40%)	2.33	1.75–3.10
Southern	2547 (48%)	12 730 (48%)	2.14	1.64–2.83

Table 1 Risk ratio of SAH according to number and type of affected relatives

	SAH patients <i>n</i> = 5282	Controls <i>n</i> = 26 402	Odds ratio	95% CI
Number of relatives with SAH				
No affected relative	5116 (96.86%)	26 030 (98.59%)	1	Reference
1 relative	156 (2.95%)	371 (1.41%)	2.15	1.77–2.59
≥ 2 relatives	10 (0.19%)	1 (0.00%)	51.0	8.56–1117*
Affected relative				
No affected relative	5116 (96.86%)	26 030 (98.59%)	1	Reference
Child	92 (1.74%)	181 (0.69%)	2.02	1.31–3.10
Sibling	46 (0.87%)	104 (0.39%)	2.40	1.72–3.34
Parent	27 (0.51%)	64 (0.24%)	2.35	1.82–3.03

*Exact confidence interval using the mid-*P* correction for discreteness of the distribution.

individuals without family history, the risk ratio was 2.15 (95% CI 1.77–2.59) for individuals with only one affected relative and 51.0 (95% CI 8.56–1117) for individuals with two or more affected relatives (Table 1). The risk associated with family history was approximately the same irrespective of type of kinship between the person at risk and the affected relative (Table 1). The effect of family history was not significantly modified by sex and age of the person at risk or by geographical region (Table 2).

Discussion

In this large population-based study, we found that having a relative with SAH increases the risk of SAH and that this risk is highly dependent on the number of affected relatives. Although the odds ratios exceeded two, with one affected relative, the absolute risk of SAH remains limited. With two or more affected relatives, a steep rise in risk was observed. This increased risk of SAH is independent of the age and gender of the person at risk, the relation with the affected relative and the gender of the affected relative. The high-risk ratio for SAH in individuals with two affected relatives implies a considerable absolute risk of SAH for such individuals. If we assume a 0.7% life-time risk of SAH in the general population (de Rooij *et al.*, 2007; Koffijberg *et al.*, 2008), the data in this study would suggest an absolute life-time risk of SAH of 26% for individuals with two or more affected relatives, with a lower confidence limit of 6%.

The increased risk of SAH in first-degree relatives of SAH patients we found in this population-based study is in line with the findings of other studies (Ronkainen *et al.*, 1993; Bromberg *et al.*, 1995; Schievink *et al.*, 1995; Gaist *et al.*, 2000; Okamoto *et al.*, 2003; Teasdale *et al.*, 2005). In previous studies, the risk of SAH in first-degree relatives was in general somewhat higher than in our study but CIs in these previous studies were wide and included the risk ratios found in the present study (Ronkainen *et al.*, 1993; Bromberg *et al.*, 1995; Schievink *et al.*, 1995; Gaist *et al.*, 2000; Okamoto *et al.*, 2003; Teasdale *et al.*, 2005). A recent study in Sweden on the risk of subarachnoid haemorrhage in siblings found a similar risk for one affected relative (Sundquist *et al.*, 2007). Our current study includes data on more individuals and is taking into account a longer period of observation. Therefore, we were able to analyse the effect of multiple affected relatives on the risk of SAH. Although we used the same databases as the previous study, overlap between these studies was limited to affected sibpairs, with one sibling affected during the year 2001. We are not aware of any studies regarding the risk of SAH in families with two or more affected relatives. As the cause of SAH is most likely multifactorial in familial as well as sporadic SAH, the risk and familial risk ratio of SAH may vary between different populations (de Rooij *et al.*, 2007). In contrast to previous studies (Schievink *et al.*, 1995; Raaymakers and MARS study group, 1999), we found the risk of SAH to be equally increased for siblings, parents and children of SAH patients.

The strength of the current study lies in the large number of patients with SAH and controls that were included. As families with two or more affected relatives are very rare, very large databases with diagnoses of hospital admissions and causes of death are needed to provide enough data to assess the risk of SAH in a population-based study. The database with information of all first-degree relatives of Swedish residents born after 1932 allowed us to assess the prevalence of SAH in relatives of affected patients. We included cases and controls from 2001 to 2005 but recorded SAH in their relatives in a much larger time span (1964–2005). Although this study provides information on the prevalence of SAH in first-degree relatives of SAH patients, it does not give any information about the incidence or prevalence of SAH in Sweden, as we identified index patients through the Swedish Inpatient Register only and not through the Cause of Death Register. Because most data in our study originate from a time before screening and preventive treatment was introduced, it is highly unlikely that the introduction of screening for intracranial aneurysms in familial SAH affected our results. Notably, had screening and preventive treatment of detected aneurysms played a role, this would have led to an underestimation of the risk in families with two or more affected relatives. To further exclude the influence of screening, we have included only patients with a diagnosis of SAH and not patients with a diagnosis of aneurysm because an unruptured aneurysm may have been detected through screening. The current study is probably a last chance to study the risk of SAH in relatives of families with two or more SAH patients because nowadays screening and preventive treatment is usually performed in such families. This will obviously alter the natural history in such families.

A potential weakness of our study is the diagnosis of SAH, which was based on ICD coding. Since the index patients with SAH were selected in 2001 through 2005, the coding will have been stable over time and the diagnosis will have been accurate as CT scans were widely available in Sweden during these years. However, for the relatives who had an SAH in earlier years, diagnosis and ICD coding could have been less reliable because CT scans were not available before the 1980s and were not available at all times during the 1980s of the 20th century. There is however no reason to believe that the inaccuracy of the diagnosis would be different between relatives of cases and relatives of controls, more so since familial aggregation of SAH has been recognized only since the mid-1990s of the 20th century (Bromberg *et al.*, 1995; Schievink *et al.*, 1995; Ronkainen *et al.*, 1997). Another issue is that we probably have not excluded all instances of perimesencephalic non-aneurysmal subarachnoid haemorrhage, not only because with older ICD coding systems it was more difficult to separate this diagnosis but also because the diagnosis was not recognized before 1985 (van Gijn *et al.*, 1985). However, we do not feel this will have influenced our results: first, because perimesencephalic SAH constitutes only 5% of

all SAHs (Flaherty *et al.*, 2005) and second, because familial perimesencephalic haemorrhage is very rare if it exists at all. In the literature, only one family with two relatives with perimesencephalic haemorrhage has been reported (Tieleman *et al.*, 2006), which may very well be a chance finding.

Another potential weakness inherent to population-based studies is that not all databases are 100% complete. If diagnoses are missing, it is possible that we have underestimated the risk of SAH due to affected first-degree relatives. On the contrary, the risk might be overestimated if the diagnosis of SAH is better-recognized in case of a positive family history. However, as SAH causes very severe and sudden symptoms, it seems unlikely that a diagnosis would go unnoticed in patients with or without family history. We therefore feel that although we cannot entirely exclude the possibility that the risk we found is overestimated by this effect, it is not very likely.

We found 2% fewer parents for the cases than for the controls. This could be caused by early death of the parents of the cases, such as one would expect in familial SAH. Also, it is possible that we missed index cases as we identified our index cases through the Swedish Inpatient Register and we did not use the Cause of Death Register for index patient identification (Huang and Van Gelder, 2002). Since familial SAH may have a worse prognosis than incidental SAH (Bromberg *et al.*, 1995), we might have missed relatively more patients with familial SAH than with sporadic SAH. Therefore, our estimates of the increased risk of SAH due to affected first-degree relatives might be conservative.

Although people with one relative with SAH have an increased risk of SAH, the absolute risk of SAH is still low. This low absolute risk underscores current recommendations that, in general, screening for aneurysms is not recommended in cases of one affected relative (MARS study group, 1999). The high risk ratio that we found for individuals with two or more affected first-degree relatives has a wide CI and provides no exact certainty about the life-time risk of SAH of these individuals. Yet, the risk ratio clearly shows that the absolute life-time risk of SAH in case of two or more affected relatives is considerable and screening for aneurysms should definitely be considered in such individuals. Because aneurysms develop during life and can also develop after initial screening, screening for aneurysms should be repeated (Wermer *et al.*, 2003). The optimal screening interval should be assessed in future studies, taking into account the irregular pattern of aneurysm development over time (Koffijberg *et al.*, 2007).

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